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# Utility of tetrathiomolybdate and tetraselenotungstate: efficient synthesis of cystine, selenocystine, and their higher homologues

Ramakrishna G. Bhat, Emmanuel Porhiel, Vadivelu Saravanan and Srinivasan Chandrasekaran*,†

*Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India*

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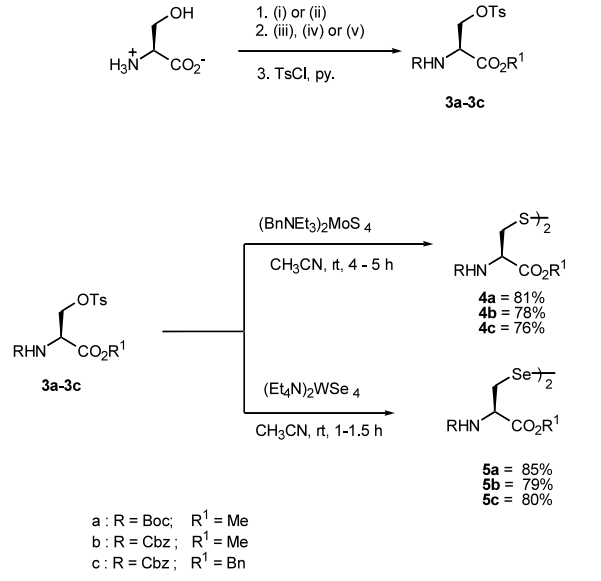
**Abstract**—Efficient synthesis of cystine, selenocystine, and their higher homologues like homo and bishomo amino acid derivatives from natural amino acid derivatives using tetrathiomolybdate and tetraselenotungstate reagents under mild and neutral conditions is reported. The generality of the reaction has been studied by capping various groups to amino and carboxyl components of canonical amino acids. © 2003 Elsevier Science Ltd. All rights reserved.

The discovery of the selenoproteins and antitumorigenic properties of selenium compounds focused attention on studies of biologically active selenocysteine containing peptides.[1–4] Selenium analogues of sulfur containing amino acids have acquired increasing importance in the study of selenium poisoning in grazing animals (alkali disease and blind staggers) and various detoxification studies.[5] Side-chain modified sulfonic analogues of aspartic and glutamic acids are potentially useful as part of the peptide effectors, such as ligand and enzyme inhibitors to increase their affinity and/or selectivity.[6] Recently, selenocystine has been used in protein ligation to incorporate selenocysteine in the active site of a metalloprotein.[7] A variety of chemical syntheses have been described[8–10] but most of them do not directly yield the diselenides (e.g. selenocystine and selenohomocystine) but rather the alkyl or aryl derivatives of selenocysteine in poor to moderate yields. There are only a few reports on the direct synthesis of selenocystine and selenohomocystine.[8,11,12] Soda et al. have reported the enzymatic synthesis of selenocystine and selenohomocystine.[13]

Schwartz and co-workers and van der Donk et al. have reported the synthesis of selenocystine in five steps starting from serine in fairly good yield.[14] Most of the reported procedures describe the use of metal selenides as key reagents in making selenocystine derivatives. Herein we report a high yielding synthesis of cystine, selenocystine and their higher homologues like homocystine, bishomocystine, selenohomocystine and selenobishomocystine from commercially available amino acids by the use of benzyltriethylammonium tetrathiomolybdate, $[(BnNEt_3)_2MoS_4]$, **1** and tetraethylammonium tetraselenotungstate, $[(Et_4N)_2WSe_4]$, **2** under mild and neutral conditions. Tetrathiomolybdate **1** has been extensively studied in our laboratory in a number of interesting transformations in organic synthesis[15] and we recently reported the use of tetra-




**Scheme 1.** *Reagents and conditions*: (i) Cbz-Cl 50% in toluene, 1N aq. $NaHCO_3$, 78%; (ii) $Boc_2O$, dioxane, 1N NaOH, 99%; (iii) MeI, $K_2CO_3$, DMF, 85%; (iv) $SOCl_2$, MeOH, 99%; (v) BnBr, benzene, DBU, 95%.

* Corresponding author. E-mail: scn@orgchem.iisc.ernet.in

† Honorary Professor, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur, Bangalore.

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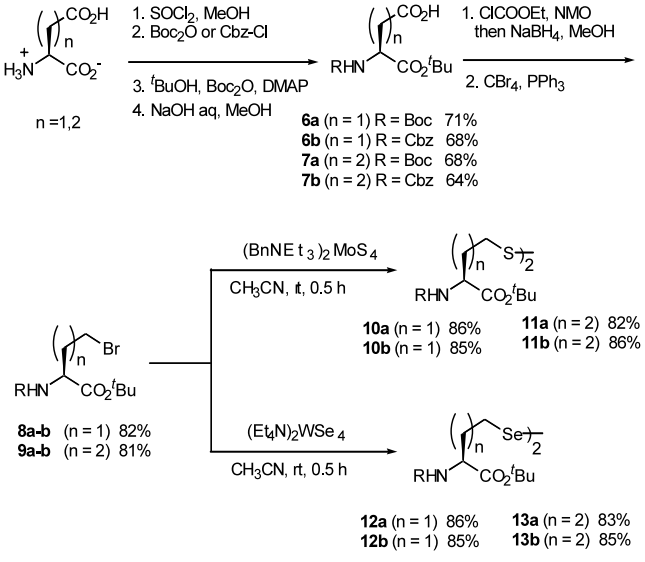
selenotungstate **2** for easy selenium transfer for the synthesis of functionalised diselenides.[16]

The amino group in serine was protected either with a benzyloxycarbonyl (Cbz) or a *tert*-butoxycarbonyl (Boc) group and the carboxyl group was protected either as a methyl ester or a benzyl ester so as to check the generality of our methodology. The side-chain hydroxyl group in these derivatives was converted to the corresponding tosylates **3a**–**c** by known procedures.[17] Treatment of these tosylates **3a**–**c** with tetrathiomolybdate, **1** (1.1 mol equiv., $CH_3CN$, 28°C, 4–5 h) resulted in the formation of the corresponding cystine derivatives, **4a**–**c**, respectively, in very good yields (76–81%). Similarly, the reaction of tosylates, **3a**–**c** with tetraselenotungstate, **2** (1.1 equiv, $CH_3CN$, 28°C, 1–1.5 h) gave the corresponding selenocystine derivatives, **5a**–**c**, respectively, in excellent yields (79–85%) (Scheme 1). The direct synthesis of cystine and selenocystine derivatives from serine has an improved overall yield in comparison to the existing routes.[12,14] The present methodology avoids the use of relatively unstable β-haloalanines which eventually lead to the formation of α,β-unsaturated amino acids.[12]

Encouraged by success in the synthesis of cystine and selenocystine it was decided to explore the utility of this methodology for the synthesis of homocystine **10a**,**b** and selenohomocystine **12a**,**b** as these molecules are known to be useful building blocks for peptide effectors.[6] Additionally there are no reports on the direct synthesis of bishomocystine **11a**,**b** and selenobishomocystine, **13a**,**b**. Readily available L-aspartic acid (Asp) was the obvious choice as the starting material for the synthesis of **10a**,**b** and **12a**,**b**. Aspartic acid was initially converted to the Boc-protected derivative **6a** or the Cbz protected derivative **6b**.[18] **6a**,**b** were then converted to the corresponding bromo compounds **8a**,**b**, respectively, via reduction with $NaBH_4$/ethyl chloroformate/NMO[19] followed by treatment with $PPh_3/CBr_4$.[20] (Scheme 2).



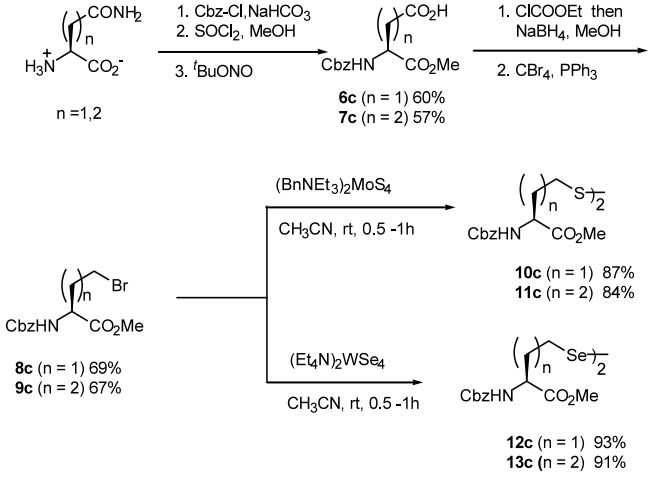

**Scheme 2.**

The bromo derivatives **8a**,**b** were subjected to a sulfur transfer reaction with tetrathiomolybdate **1** (1.1 equiv., $CH_3CN$, 28°C, 30 min) and the corresponding homocystine derivatives **10a**,**b**, respectively, were obtained in high yields (85–86%). Similarly the reaction of bromo compounds **8a**,**b** with tetraselenotungstate **2** (1.1 equiv., $CH_3CN$, 28°C, 30 min) afforded the corresponding selenohomocystine derivatives **12a**,**b** in very good yields (85–86%) (Scheme 2).

The same strategy was further extended to the synthesis of bishomocystine derivatives **11a**,**b** from bromo compounds **9a**,**b** using tetrathiomolybdate **1** as well as to the synthesis of selenobishomocystine derivatives **13a**,**b** from bromo compounds **9a**,**b** using tetraselenotungstate **2** (Scheme 2). The precursors **9a**,**b** were derived readily from glutamic acid.[18–20]

In another approach it was demonstrated that amino acids like aspargine (Asn) and glutamine (Gln) can also be used as starting materials for the synthesis of homocystine, selenohomocystine and their higher homologues. Taking advantage of the reaction of amides with *tert*-butyl nitrite,[21] the protected derivatives of aspargine (Asn), **6c** and glutamine (Gln), **7c** were converted to the corresponding bromo compounds **8c** and **9c**, respectively, in high yields. Following essentially the same protocol described earlier **8c** and **9c** were converted efficiently to homocystine **10c** and bishomocystine **11c** and selenohomocystine **12c** and selenobishomocystine derivatives **13c**, respectively, in high yields (Scheme 3).

In conclusion we have demonstrated the utility of tetrathiomolybdate **1** and tetraselenotungstate **2** for a short, easy and high yielding synthesis of optically pure cystine, selenocystine and their higher homologues under mild and neutral conditions starting from commercially available amino acids. The easy conversion of tosylates into disulfides and diselenides would be very useful in peptide synthesis where one can use serine as a substitute for cysteine avoiding the use of an additional protecting group and aerial oxidation of the sulfhydryl group. Further work is in progress to expand




**Scheme 3.**

the scope of these new reagents in the synthesis of cyclic peptides.

**Spectral data of selected compounds**:

*Dimethyl bis (N-benzyloxycarbonyl)-L-homocystine* ***(10c)***: $^1$H NMR (300 MHz, $CDCl_3$, 25°C): $\delta$ 7.35 (s, 10H, 2×Ph), 5.49 (d, 2H, 2×N*H*, $J=7.5$ Hz), 5.1 (s, 4H, 2×C$H_2$Ph), 4.52–4.46 (m, 2H, 2×C*H*), 3.76 (s, 6H, 2×C$H_3$), 2.70 (t, 4H, 2×C$H_2$S, $J=6.9$ Hz), 2.30–2.17 (m, 2H, 2×[HC$H_a$]CH), 2.11–2.0 (m, 2H, 2×[HC$H_b$]CH); $^{13}$C NMR (75.45 MHz, $CDCl_3$, 25°C): $\delta$ 172.3 (*C*$O_2$$CH_3$), 156.0 (N*C*$O_2$), 136.0 (Ph), 128.5 (Ph), 128.2 (Ph), 128.1 (Ph), 67.1 (*C*$H_2$Ph), 52.9 (O*C*$H_3$), 52.6 (*C*H), 34.3 (*C*$H_2$S), 32.3 (*C*$H_2$CH); $C_{26}H_{32}N_2O_8S_2$, calcd mass: 564, FABMS $m/z$: 565 $(MH)^+$.

*Dimethyl bis (N-benzyloxycarbonyl)-L-selenohomocystine* ***(12c)***: $^1$H NMR (300 MHz, $CDCl_3$, 25°C): $\delta$ 7.34 (s, 10H, 2×Ph), 5.48 (d, 2H, 2×N*H*, $J=7.8$ Hz), 5.10 (s, 4H, 2×C$H_2$Ph), 4.52–4.46 (m, 2H, 2×C*H*), 3.75 (s, 6H, 2×C$H_3$), 2.91 (t, 4H, 2×C$H_2$Se, $J=7.1$ Hz), 2.34–2.23 (m, 2H, 2×[HC$H_a$]CH), 2.15–2.03 (m, 2H, 2×[HC$H_b$]CH); $^{13}$C NMR (75.45 MHz, $CDCl_3$, 25°C): $\delta$ 172.2 (*C*$O_2$$CH_3$), 156.0 (N*C*$O_2$), 136.1 (Ph), 128.5 (Ph), 128.2 (Ph), 128.1 (Ph), 67.1 (*C*$H_2$Ph), 53.6 (O*C*$H_3$), 52.6 (*C*H), 34.2 (*C*$H_2$Se), 24.7 (*C*$H_2$CH); $C_{26}H_{32}N_2O_8Se_2$, calcd mass: 660, FABMS $m/z$: 698 $(MK)^+$.

*Dimethyl bis (N-benzyloxycarbonyl)-L-bishomocystine* ***(11c)***: $^1$H NMR (300 MHz, $CDCl_3$, 25°C): $\delta$ 7.35 (s, 10H, 2×Ph), 5.40 (d, 2H, 2×N*H*, $J=7.8$ Hz), 5.11 (s, 4H, 2×C$H_2$Ph), 4.41–4.39 (m, 2H, 2×C*H*), 3.75(s, 6H, 2×C$H_3$), 2.66–2.64 (m, 4H, 2×C$H_2$S), 1.96–1.91 (m, 2H, 2×{HC$H_a$}CH), 1.75 (m, 6H, 2×[C$H_2$CH$_2$CH and $CH_2$ {HC$H_b$}CH]); $^{13}$C NMR (75.45 MHz, $CDCl_3$, 25°C): $\delta$ 172.7 (*C*$O_2$$CH_3$), 155.9 (N*C*$O_2$), 136.1 (Ph), 128.5 (Ph), 128.2 (Ph), 128.1 (Ph), 67.0 (*C*$H_2$Ph), 53.4 (O*C*$H_3$), 52.5 (*C*H), 37.8 (*C*$H_2$S), 31.3 (*C*$H_2$), 24.7 (*C*$H_2$CH); $C_{28}H_{36}N_2O_8S_2$, calcd mass: 592, FABMS $m/z$: 593 $(MH)^+$.

*Dimethyl bis (N-benzyloxycarbonyl)-L-selenobis homocystine* ***(13c)***: $^1$H NMR (300 MHz, $CDCl_3$, 25°C): $\delta$ 7.35 (s, 10H, 2×Ph), 5.44 (d, 2H, 2×N*H*, $J=8.1$ Hz), 5.11 (s, 4H, 2×C$H_2$Ph), 4.44–4.39 (m, 2H, 2×C*H*), 3.75 (s, 6H, 2×C$H_3$), 2.86–2.82 (m, 4H, 2×C$H_2$Se), 2.05–1.94 (m, 2H, 2×{HC$H_a$}CH), 1.77 (m, 6H, 2×[C$H_2$CH$_2$CH and $CH_2${HC$H_b$}CH]); $^{13}$C NMR (75.45 MHz, $CDCl_3$, 25°C): $\delta$ 172.7 (*C*$O_2$$CH_3$), 155.9 (N*C*$O_2$), 136.1 (Ph), 128.5 (Ph), 128.1 (Ph), 128.0 (Ph), 67.0 (*C*$H_2$Ph), 53.3 (O*C*$H_3$), 52.4 (*C*H), 32.2 (*C*$H_2$Se), 28.5 (*C*$H_2$), 26.5 (*C*$H_2$CH); $C_{28}H_{36}N_2O_8Se_2$, calcd mass: 688, FABMS $m/z$: 689 $(MH)^+$.

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